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Damage in peripheral nerve from continuous electrical stimulation: comparison of two stimulus waveforms

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Abstract—*The propensity for two types of charge-balanced stimulus waveforms to induce injury during eight hours of continuous electrical stimulation of the cat sciatic nerve was investigated. One waveform was a biphasic, controlled-current pulse pair, each phase 50 μs in duration, with no delay between the phases ('short pulse', selected to excite primarily large axons), whereas in the second type each phase was 100 μs in duration, with a 400 μs delay between the phases (selected to excite axons of a broader spectrum of diameters). The sciatic nerve was examined for early axonal degeneration (EAD) seven days after the session of continuous stimulation. With both waveforms, the threshold stimulus current for axonal injury was greater than the current required to excite all of the nerve's large axons. The correlation between simple stimulus parameters and the amount of EAD was poor, especially with the 'short pulse' waveform, probably due to variability between animals. When the stimulus was normalised with respect to the current required to fully recruit the large axons, a good association between damage and stimulus amplitude emerged. The damage threshold was higher for the 'short pulse' waveform. The implications for clinical protocols are discussed.*

Keywords—*Cat, Electric stimulation, Evoked potentials, FES, Nerve damage, Peripheral nerve, Pulse duration, Sciatic nerve*

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1 Introduction

THE PRESENT study was conducted as part of our programme to develop stimulation protocols for brain and peripheral nerves that embody the highest possible margin of safety. Previous studies conducted in our laboratory have shown the importance and interaction of several parameters in the induction of injury to peripheral nerves during prolonged electrical stimulation, including total duration of the stimulation, stimulus frequency (pulse pair repetition rate), stimulus duty cycle and stimulus pulse amplitude (AGNEW *et al.*, 1989). When we first set out to study the mechanisms underlying stimulation-induced neural damage, we selected a stimulus waveform which would efficiently excite axons with a wide range of diameters. For this purpose, we used a charge-balanced, biphasic, rectangular pulse pair, in which each phase of the pair was 100 μs in duration, and in which the first and second phases were separated by a rather long interphase delay of 400 μs (called the 'long pulse' in subsequent sections of the paper). Thus, the duration of each pulse is longer than, or comparable to, the chronaxies of most of the myelinated axons in mammalian peripheral nerves (RANCK, 1975), and the interphase delay prevents quenching of nascent action potentials evoked in smaller myelinated axons by the charge-balancing second phase (GORMAN and MORTIMER, 1983).

Previous studies showed that the stimulation-induced injury in peripheral nerves is linked to the induced neuronal activity, whereas other work indicated that the activity-related injury must be mediated at least in part via 'mass-action' phenomena, in which the injury to individual axons is due at least in part to the induced hyperactivity in a large number of axons (AGNEW *et al.*, 1990). We therefore wished to determine if injury to the *large* axons could be reduced by using a waveform which excites *large* axons efficiently, but excites *small* axons relatively less efficiently, i.e. a waveform for which the ratio of the stimulus amplitude required to excite the small axons rather than the large axons is greater than the ratio for our standard test waveform. For this purpose, we selected a biphasic charge-balanced waveform in which each phase was of the shorter duration of 50 μs and with no interphase delay (called the 'short pulse' in the rest of the paper).

2 Materials and methods

Under general anaesthesia, electrodes of our own design and manufacture (the HMRI bidirectional helical electrode array) were implanted around both sciatic nerves of adult cats of both sexes. The position of the electrode was approximately 2–3 mm proximal to the tibial-peroneal bifurcation. The electrode comprised a pair of platinum bands, 0·5 mm in width, and approximately 9 mm in length (sufficient to completely encircle the nerve). The ribbons

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are supported on the inner circumference of a matrix of silicone elastomer, which uncoils slightly as the array is installed on the nerve. Thus, the platinum electrodes tend to remain in close contact with the nerve around its entire perimeter (NAPLES *et al.*, 1990).

A pair of recording electrodes was also implanted subcutaneously over the spinal cord to record the compound action potentials evoked in the sciatic nerve by the stimulating electrode. One recording electrode was sutured to the subcutaneous fascia directly over the spinal cord at approximately the L4–5 level, and the other member of the bipolar pair was sutured to the fascia approximately 5 cm caudally. With this arrangement, the compound action potentials evoked in the left or right nerve can be recorded with a single pair of electrodes.

Three weeks after the implant surgery, the cats were again anaesthetised with pentobarbital and one or both sciatic nerves was stimulated continuously for eight hours at 50 Hz, using either the 'long or short' pulses described in the Introduction.

Prior to the start of the eight hours of continuous stimulation, we measured the recruitment characteristics of the compound action potential evoked by the stimulating electrodes and recorded over the spinal cord. The averaged evoked compound action potential (AECAP) was obtained by summing 64–128 consecutive nerve responses. To generate the recruitment characteristics of the large, early component of the AECAPs (the α-component) the nerve was stimulated at each of several amplitudes, and the amplitude of the positive phase of the α component was plotted against the stimulus pulse amplitude.

Seven days after stimulation, the animals were again anaesthetised with pentobarbital, and perfused through the ascending aorta with 2 litres of Karnovsky's fixative (2·0 per cent paraformaldehyde and 2·5 per cent glutaraldehyde in 0·1 M sodium cacodylate buffer solution) using a peristaltic perfusion pump (Cole-Palmer model 7520-25). Following perfusion, the tissues were further fixed, with electrode arrays *in situ*, until autopsy the following day. At autopsy, the electrodes were exposed and photographed to document the position of the electrodes and leads and any evidence of compression or distortion of the sciatic nerves.

The specimens for light microscopy were processed and embedded in Polybed plastic (Polysciences). Sections 1 μm in thickness were stained with Toluidine Blue-Azure II. The sections were examined to determine the thickness and composition of the epineurium, the amount of connective tissue between the electrodes and the nerve, evidence of haemorrhage or infection, and increased endoneurial connective tissue. The extent and severity of axonal damage was determined, and specific features noted (i.e. axonal degeneration or loss, remyelination and presence of macrophages). In cross-sections of the nerve, early axonal degeneration (EAD) is characterised by collapse of the myelin into the axoplasmic space (AGNEW *et al.*, 1989). The total number of myelinated axons and axons undergoing EAD seven days after stimulation were counted in control and stimulated nerves from sites beneath the proximal electrode. These counts were made manually from montages of thick-section micrographs having a final magnification of 325.

The percentage of myelinated axons undergoing EAD was plotted against the stimulus pulse amplitude, which was expressed either as the pulse current, as the charge per pulse phase (pulse current × pulse duration) or as multiples of the current required to induce full recruitment of the earliest component of the AECAP recorded over the spinal cord. The association between the stimulus and the amount of EAD was quantified as the coefficient of determination r (HERDAN, 1955). This describes how closely the dependent variable (percentage of axons undergoing EAD) is linked to the stimulus amplitude. It is calculated as

$$r = (\sum xy - nXY)/[(\sum x^2 - nX^2)(\sum y^2 - nY^2)]^{1/2}$$

where x is the particular representation of the stimulus amplitude and y is the percentage of myelinated axons undergoing EAD beneath the proximal pole of the electrode. X and Y designate the means of x and y, respectively, and n is the number of nerves in the group.

3 Results

Fig. 1 shows a cross-section of an electrically damaged sciatic nerve, following stimulation with a 'short pulse' waveform. Axons in several stages of EAD are randomly scattered throughout the cross-section of the nerve beneath the proximal electrode. By one week after stimulation, there was a similar distribution of EAD 1 cm proximal and 0·5 and 1 cm distal to the electrodes. Irreversible damage to at least *some* of the axons undergoing EAD is indicated by the presence of myelin ovoid bodies and subsequent degradation, including ingestion of fragments of myelin by macrophages by 3–4 weeks after stimulation (AGNEW *et al.*, 1989).

Fig. 2*a* shows a series of AECAP's evoked by stimulation of the sciatic nerve with the short pulse waveform. The amplitude of each phase of the stimulus pulse pair is indicated at the left of each AECAP. The AECAP is domi-

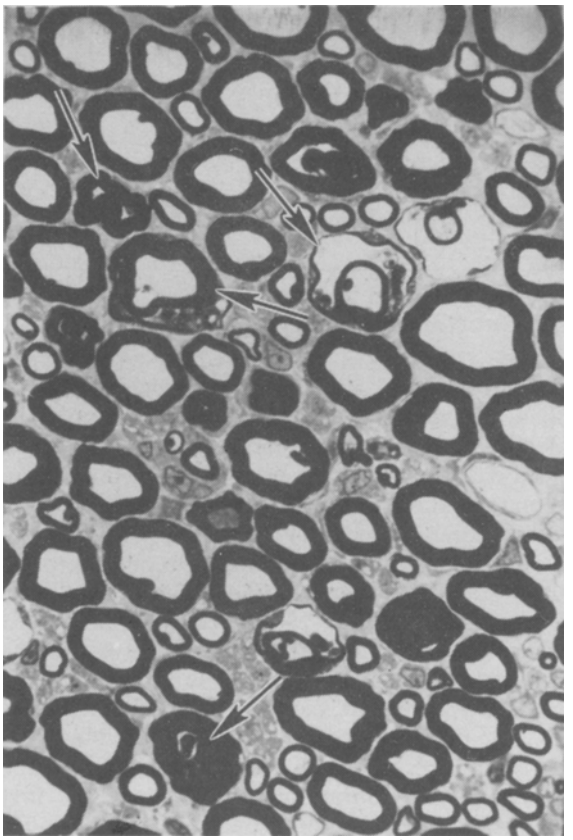

Fig. 1 *1 μm thick plastic cross-section of right sciatic nerve beneath proximal electrode. The nerve was pulsed for 8 h using 3200 μA at 50 Hz (approximately 3·2 times full α recruitment) and pulse duration of 50 μs (short pulse waveform). The animal was sacrificed one week later. Myelinated axons undergoing early axonal degeneration (EAD) are scattered through the cross-section of the nerve. Some typical EAD profiles are indicated by arrows. In some instances, myelin delamination or loss is extensive. There was approximately 1 per cent incidence of EAD over the entire cross-section of the nerve. Toluidine Blue-Azure II. Magnification is × 750*

nated by an early component that reaches its peak approximately 1 ms after the start of the stimulus pulse pair. This is designated the α-component which, for cat peripheral nerve, is known to be comprised of the action potentials from the Group I and the Group II axons of the nerve's motor branches and the β-component of the cutaneous branches (RUCH and FULTON, 1960). These axons have overall diameters of approximately 5–22 μm.

The inflection on the falling phase of the α-component of the AECAP shows that it is composed of action potentials from axons of two broad modalities. Thus, full recruitment of the α-component corresponds to excitation of all of the Group I and Group II axons in the sciatic nerve. The amplitude of the α-component was quantified as the distance between the trace and the broken line indicated on the lower trace in Fig. 2*a*. The broken line is an estimate of the 'local' baseline of the trace.

slowly conducting myelinated axons (the Group III axons of the nerve's motor branches and the δ-fibres of the cutaneous branches) is difficult to discern when the electrode is implanted on the sciatic nerve, although it is fairly prominent in the AECAPs shown in Fig. 2*b*. It is designated 'δ' in accordance with the accepted nomenclature for cutaneous nerves (although we recognised that the sciatic nerve is comprised of a mixture of deep and cutaneous branches).

The three AECAPs shown in Fig. 2*b* were evoked by charge-balanced pulse pairs, each phase being 100 μs in duration but with different interphase intervals. As the interphase interval beween the first and second phases of the pulse pair was increased, the amplitude of the α-component and the latency of the δ-component did not change but the amplitude of the latter increased greatly. Thus, we conclude that the δ-peak does indeed represent

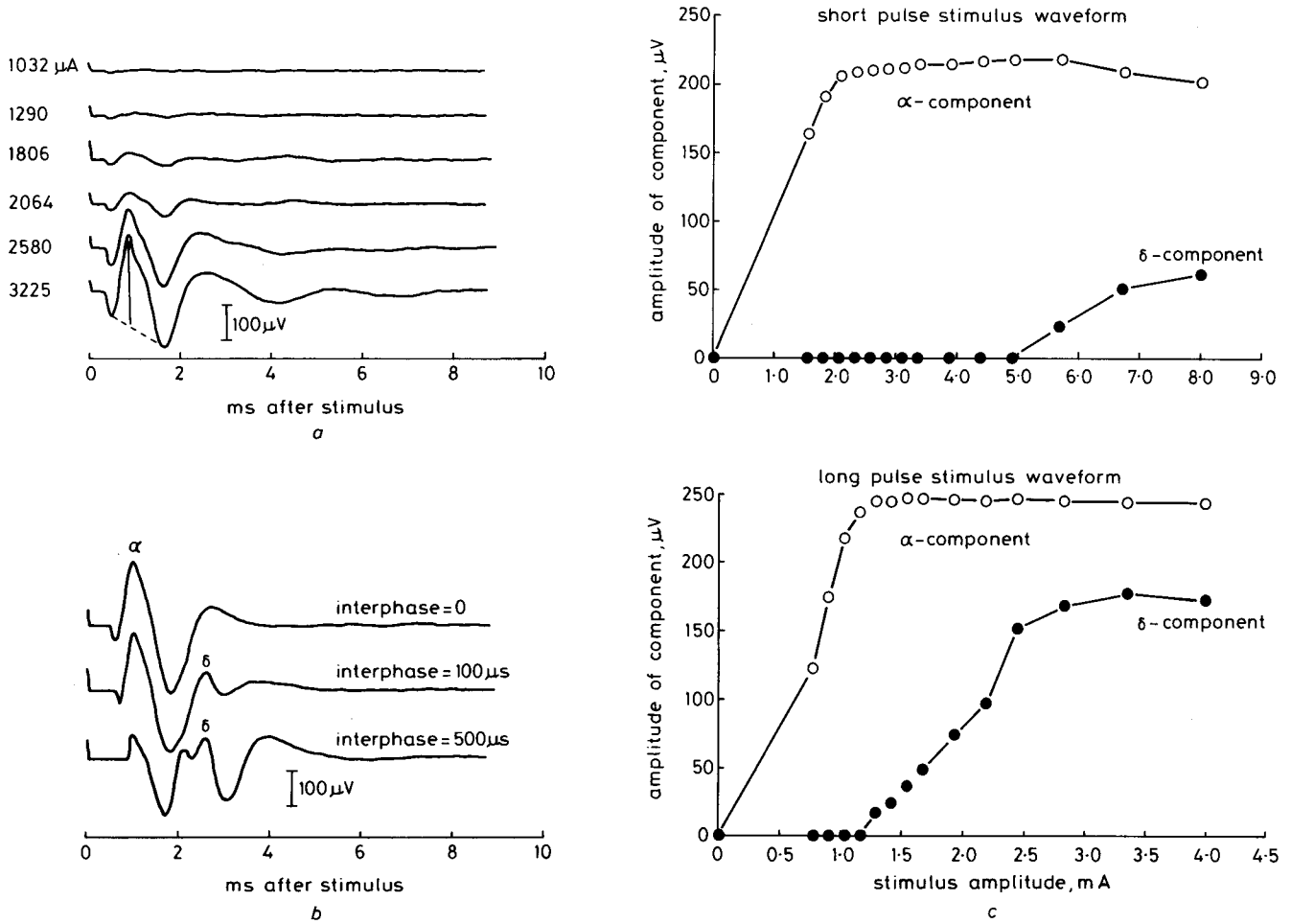

Fig. 2 *(a) Averaged evoked compound action potentials (AECAPs) evoked by the stimulating electrode on the sciatic nerve and recorded with a pair of electrodes over the lumbosacral spinal cord. The AECAPs were evoked using the short pulse waveform (50 μs per phase, no interphase delay) whose pulse amplitude is given at the left of each tracing. The amplitude of the α-component is the distance between the broken line (connecting the inflections at the beginning and end of the positive phase of the component) and the peak of the positive phase, as indicated in the bottom trace. (b) AECAPs evoked using pulses of 100 μs per phase, and with various intervals between the first and second phases of the pulse pair. As the interphase interval was lengthened, a second component (δ) emerged, whose latency was independent of the interphase interval. In the lower trace, part of the α-component has been blanked by the artefact-suppression circuitry. (c) Recruitment curves for the α- and δ-components of the AECAP from another cat, showing the preferential recruitment of the α-component by the short pulse stimulus waveform*

This method of quantifying the amplitude of the α-component is quite immune to error due to the curvature in the trace's baseline during the recovery from the stimulus artefact. Also, the positive phase of the α-component is not contaminated by the compound action potentials of more slowly conducting axons, the earliest of which is superimposed on the end of the negative phase of the α-component (Fig. 2*b*).

The peak due to action potentials evoked in more

the action potentials in small myelinated axons, rather than action potentials induced at an ectopic location on the nerve by the second phase of the stimulus pulse pair.

Fig. 2*c* shows the recruitment characteristics of the α- and δ-components of the AECAP from one cat. The values for the amplitude of the δ-component are only estimates, due to the superposition of this component onto the end of the α-component. For the short pulse stimulus (top), the threshold of the δ-component is approximately 2·5 times

greater than the full recruitment current of the α-component. For the long pulse waveform, the threshold of the δ-component is approximately the same as the full recruitment current of the α component.

Figs. 3*a* and 3*b* show the recruitment characteristics of the α-component of the AECAPs from one sciatic nerve, using the long pulse and the short pulse waveform. With the short pulse waveform, a higher pulse current (Fig. 3*a*), but less charge per phase (Fig. 3*b*) was required to fully recruit the α-component, but the maxima of the two curves were nearly identical. This indicates that both waveforms are capable of fully recruiting the Group I and Group II axons in the sciatic nerve.

Fig. 3*c* shows recruitment characteristics of the α-component of the AECAPs from four sciatic nerves from four cats. The long pulse waveform was used to evoke the AECAPs. In most cases the stimulus pulse current (the abscissa) required to fully recruit the α-component is quite well defined; animal 4, in which this current is rather ill defined, is exceptional. The current required to fully recruit the α-component, however, is quite variable across animals.

Fig. 4*a* shows data from 24 sciatic nerves from 20 cats, and depicts the percentage of the myelinated axons undergoing EAD seven days after the eight hours of continuous stimulation. The same data are shown in Figs. 4*a*, *b*, and *c*, but in Fig. 4*a* the stimulus is expressed as the pulse current, in Fig. 4*b* as the charge delivered in each phase of the pulse pair, and in Fig. 4*c* as multiples of the stimulus

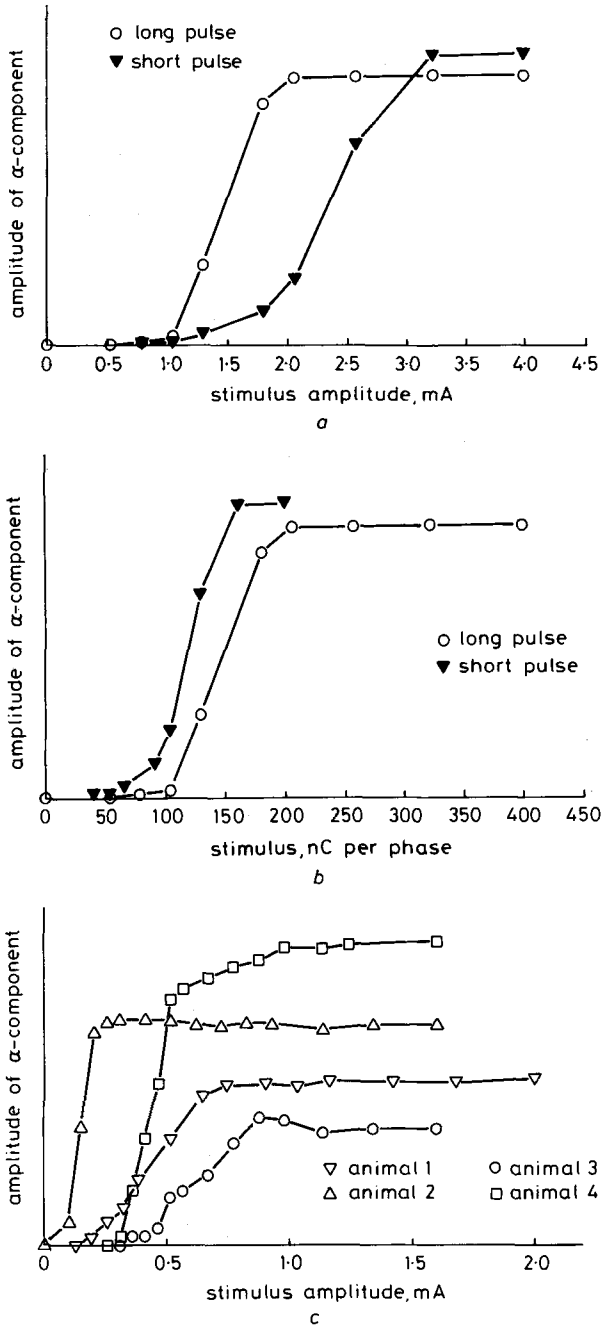

Fig. 3 *(a) Recruitment characteristics of the α-component of the AECAPs evoked with the short and long pulse waveforms. (b) The same data, using charge per phase of the stimulus pulse pair as the abscissa. (c) Recruitment characteristics of the α-component of the AECAPs from four cats, to show variability in the threshold and full recruitment current between animals*

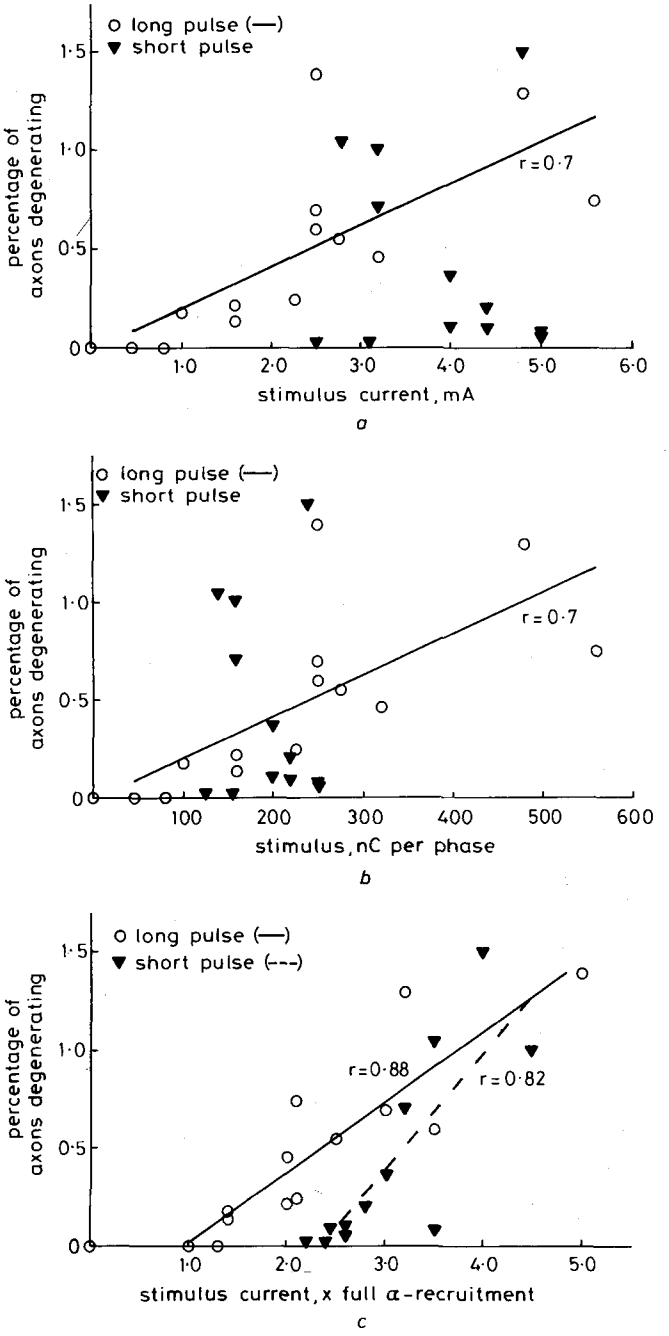

Fig. 4 *Plots of the percentage of myelinated axons in the sciatic nerve undergoing EAD 7 days after 8 h of stimulation, against (a) the stimulus pulse amplitude, (b) the stimulus pulse charge per phase and (c) the stimulus pulse amplitude expressed as multiples of the current required to fully recruit the α-component of the AECAP. The first-order regression lines and the corresponding coefficients of determination (r) are shown in (c) for the data from both stimulus waveforms. These are also shown in (a) and (b) for the long pulse waveform*

pulse current required to fully recruit the α-component of the AECAP. The first-order regression lines are shown for the long pulse waveform (and in Fig. 4*c* for the short pulse waveform). The coefficients of determination (r) for the long pulse and for the short pulse groups are also given.

For both the long and the short pulse waveforms, there is fairly good correlation between the number of axons undergoing EAD and the stimulus amplitude, when the latter is expressed as multiples of the full recruitment current for the long and short pulse waveform (Fig. 4*c*, $r = 0{\cdot}88$, $r = 0{\cdot}82$). When the stimulus amplitude is so normalised, the threshold for axonal injury is quite well defined and is higher for the short pulse waveform. However, the regression line is steeper for the short pulse waveform, and the data points for the two waveforms are interspersed when the stimulus current exceeds approximately three times the current required for full α-recruitment. In Fig. 4*c*, the damage threshold for the short pulse waveform is between 2·2 and 2·6 × full α-recruitment current.

To test the hypothesis that the threshold for the long pulse waveform is lower than for the short pulse waveform, we compared the means of amount of EAD for the five nerves receiving the long pulse waveform and the five receiving the short pulse waveform for which the stimulus current was 2·2 to 2·6 × full α-recruitment. The means of the two groups were significantly different ($Y_{short} = 0{\cdot}038$ per cent, $Y_{long} = 0{\cdot}446$ per cent, $t = 3{\cdot}9$, $df = 4$, $p < 0{\cdot}01$), indicating that Y_{long} is significantly larger than Y_{short} over this part of the x-axis (i.e. the threshold is higher for the short pulse).

When the stimulus amplitude is not normalised (Figs. 4*a* and 4*b*) there is still a fair correlation between the amount of EAD and the stimulus amplitude for the long pulse waveform ($r = 0{\cdot}7$), but almost no correlation between EAD and pulse amplitude for the short pulse waveform ($r = 0{\cdot}108$).

4 Discussion

This study compared the extent of the axonal damage resulting from eight hours of continuous stimulation of the sciatic nerve with each of two charge-balanced stimulus waveforms, the first of which was selected to excite axons of a wide range of diameters whereas the second was selected to restrict somewhat the excitation of smaller axons.

In some clinical applications of functional electrical stimulation, such as a lower-extremities gait assistance device or upper extremities motor prosthesis, only the axons of the α-motoneurons need be excited. Their axons are of Group I and Group II calibre, whose action potentials are represented in the α-component of the AECAP. Thus, the threshold for axonal injury, when expressed as multiples of full α-recruitment, defines a margin of safety for the particular stimulus waveform and stimulation protocol. Although the protocol used in the present study is not typical of those used with motor protheses, our findings do suggest that the margin of safety will be higher if a waveform similar to the short pulse is used, i.e. a stimulus in which the first phase of the waveform is quite short and is followed immediately by the charge-balancing second phase. We should note that this would not be the case for applications where clinical efficacy requires that smaller myelinated axons be excited, e.g. stimulation of the pudendal nerve to effect voiding of the bladder (DEGROAT and BOOTH, 1980; TANAGHO *et al.*, 1982).

Fig. 4 illustrates that, to obtain an index of the relative safety of a particular stimulus waveform, the stimulus amplitude must be normalised on some function which accounts for the variability with which the stimulus current is coupled into the nerve. Fig. 3*c* illustrates that this coupling can be quite variable, even with a completely circumneural electrode incorporated into a self-sizing matrix. This is probably due to the formation of various amounts of connective tissue between the electrode and the epineurium, and around the electrode. Without such normalisation and with a stimulus waveform for which the slope of the damage curve is steep (as is the case with the short pulse waveform), then a threshold for neural damage cannot be estimated. As shown in Fig. 4*c*, use of the full α-recruitment current as the normalising function works fairly well, even when the slope of the damage curve is steep. While unanaesthetised patients with an intact neuraxis would probably not tolerate even a brief period of stimulation at an intensity sufficient to define the upper portion of the recruitment curve of the neurogram, this should present no problem for patients with complete or nearly complete spinal lesions.

Previous studies conducted in our laboratory strongly suggest that the stimulation-induced injury is linked to the neural activity induced by the stimulation. Blocking the action potentials in most of the axons by infusing local anaesthetic over the stimulating electrode protected all of the axons in the nerve from stimulation-induced injury (AGNEW *et al.*, 1990). These findings must be reconciled with the results from the present study. Axons of a wide range of diameters undergo EAD one week after the eight hours of stimulation, but most of these have overall diameters of approximately 5–15 μm. Thus, they include many Group I and Group II axons whose action potentials contribute to the α-component of the AECAPs. However, with the long pulse or the short pulse waveform, the damage threshold current is greater than that required to fully recruit the α-component.

Furthermore, Fig. 4*c* shows that even when the stimulus amplitude is normalised on the full α-recruitment current, the thresholds and slope of the damage curve is different for different stimulus waveforms. Were the injury to any particular large axon due only to the action potentials induced in that axon, then in Fig. 4*c* the threshold of the damage should be identical for both types of stimulus waveforms. Clearly, this is not the case. However, the damage to any particular axon might be linked to the induced neuronal activity *en masse*, and involve the activity induced in the smaller axons as well as those represented in the α-component of the compound action potential. Figs. 2*b* and 2*c* show that, without the interphase delay, the smaller myelinated axons are not readily excited. It may be the activity evoked in these smaller axons by the broad-spectrum (long pulse) waveform, in conjunction with the activity in the larger axons, which engenders injury via 'mass action', perhaps by an activity-related change in the composition of the extracellular fluid. Unfortunately, unlike the α-component, the amplitude of the δ-component of the CAP is difficult to quanitfy, particularly across animals. It is superimposed on the last part of the negative phase of the α-component, whose amplitude is also dependent upon the stimulus amplitude.

It is also possible that the damage is due (at least in part) to electrochemical processes at the electrode/tissue interface. Evolution of toxic products at the interface would be more likely with the long pulse waveform, because the longer duration of each pulse phase, and the delay between the first and the second phases of the pulse pair, would permit toxic species generated during the first phase to diffuse away from the interface before reaction could be reversed by the charge-balancing second phase (ROBBLEE and ROSE, 1990). Furthermore, with the short

pulse waveform, the α-component of the AECAPs can be fully recruited with less charge per phase (and thus also at a lower charge density) (Fig. 3*b*). It is this economical use of charge per phase (and thus also of charge density), which led other authors to suggest that short pulses (or pulse pairs) would imbue a stimulation protocol with a higher margin of safety (CRAGO *et al.*, 1974). However, the studies cited above, in which superfusion of the nerve and stimulating electrode with local anaesthetic prevented stimulation-induced injury, argues strongly against the axonal damage being due exclusively to electrochemical events at the electrode/tissue interface, although they do not exclude the possibility that these phenomena may act as a costressor in conjunction with the induced neuronal activity.

Fig. 4*b* shows that damage may occur at a moderate charge per phase and a very low charge density (approximately 150 nC per phase, and with the electrodes' geometric surface area of 4·5 mm^2, at a charge density of approximately 3·2 $\mu C\,cm^{-2}$). It has never been established that potentially dangerous electrochemical reactions do not occur *in vivo* even at very low charge densities. However, in the cerebral cortex, using pulse pairs whose overall duration was comparable to those of the long pulse waveform used here, and with comparable stimulus frequency and total time of stimulation, the charge density had to exceed 50 $\mu C\,cm^{-2}$ at 1000 nC per phase in order to induce histologically detectable neural injury (MCCREERY *et al.*, 1990; YUEN *et al.*, 1981).

It is coincidental that the types of stimulus waveforms which minimise the hazard of electrochemical reactions at the electrode/tissue interface (a pair of short, charge-balanced pulses with no interphase delay) are also the waveforms which would tend to excite large axons in preference to smaller axons or, more generally, neural elements with short chronaxies. This, in turn, would reduce neural injury deriving from the induced neuronal mass action. This covariance of the magnitude of the potential electrochemical hazard and the tendency for a stimulus waveform to excite axons of a wide range of calibres must be borne in mind as we seek to better understand the mechanisms by which prolonged electrical stimulation may damage neurons and axons in brain or peripheral nerves.

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Douglas B. McCreery received the BS degree in Electrical Engineering from the University of Connecticut (Storrs, Connecticut, USA) in 1967, and the Ph.D. degree in Physiology in 1973 from the same institution. He is now a neurophysiologist in the Neurological Research Laboratory, Huntington Medical Research Institutes, Pasadena, California, where his research interests include the responses of nervous tissue to electrical stimulation and the development of stimulating electrodes for neuroprostheses.

William F. Agnew received the BA degree in Zoology from Wheaton College, Illinois, USA, in 1949, the MS degree in Physiology from the University of Illinois in 1954 and the Ph.D. degree in Physiology from the University of Southern California, Los Angeles, in 1964. He is the Director of Neurological Research, Huntington Medical Research Institutes, Pasadena, California. His present research includes the effects of electrical stimulation on the central and peripheral nervous system and the development of neural prosthetic devices.

Dr Ted Yuen received a Ph.D. in Experimental Pathology in 1969 from the USC School of Medicine, Los Angeles, California, USA. From 1971 until the present, his work at the Huntington Medical Research Institute, Pasadena, California has included the structure and function of the choroid plexus as well as the response of cat brain and peripheral nerve following electrical stimulation. His other studies at HMRI have assessed the biocompatibility of polymers and metals in nervous tissues.

Leo Bullara received the BA in Physics from the University of Southern California in 1955. Since 1966, he has been a physicist at the Huntington Medical Research Institutes in Pasadena, California. His research has included electrical stimulation of the nervous system and the design of neural electrodes and various neurosurgical instruments.